**Actinic keratosis: ingenol mebutate gel**

**Evidence summary**
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nice.org.uk/guidance/esnm14

**Overview**

The content of this evidence summary was up-to-date in March 2013. See summaries of product characteristics (SPCs), British national formulary (BNF) or the MHRA or NICE websites for up-to-date information.

**Key points from the evidence**

Ingenol mebutate gel (Picato) is a macrocyclic diterpene ester licensed for the cutaneous treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis in adults. It received a European marketing authorisation in November 2012 and was launched in the UK in January 2013.

Guidance on actinic keratosis from the British Association of Dermatologists, the European Dermatology Forum and the Primary Care Dermatology Society pre-dates the availability of ingenol mebutate gel. Depending on clinical presentation, treatment of actinic keratosis may be targeted at individual lesions, or field-directed treatment may be used for larger areas of skin with multiple lesions. Therapies include ablative procedures, photodynamic therapy and a number of topical treatments.

Ingenol mebutate gel is a patient-applied, topical, field-directed treatment for actinic keratosis. Two strengths are licensed: 150 micrograms/gram (0.015%) for treating lesions of the face or scalp, and 500 micrograms/gram (0.05%) for treating the trunk or extremities. The duration of the treatment course, which is a once-daily application for 2 consecutive days for the trunk or extremities, and once daily for 3 consecutive days for the face or scalp, is shorter than that for other patient-applied, topical medicines licensed for this condition.
In phase III, double-blind, randomised, vehicle-gel controlled trials of patients with actinic keratosis, ingenol mebutate gel was associated with significantly higher rates of complete lesion clearance in the treatment area, compared with vehicle gel. In pooled analyses of these studies, the percentages of patients with complete clearance of lesions after treatment with ingenol mebutate gel were 42.2% (face/scalp studies) and 34.1% (trunk/extremities studies), compared with 3.7% and 4.7% respectively of patients receiving vehicle gel (p<0.001 in both cases).

The most common treatment-related adverse events reported in the phase III studies were skin responses at the site of application.

Local decision makers will need to consider the place of ingenol mebutate gel alongside other available treatments for actinic keratosis. The publication of direct head-to-head studies with other treatments would enable its place in therapy to be more clearly established. The authors of a 2012 Cochrane review concluded that field-directed treatments for actinic keratosis, which included ingenol mebutate gel, had similar efficacy. However, adverse events and cosmetic outcomes varied, and more direct comparisons between treatments are needed to determine optimal therapeutic approaches.

**Key evidence**


**About this evidence summary**

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, but this summary is not NICE guidance.

**Relevance to NICE guidance programmes**

Ingenol mebutate gel was not considered appropriate for a NICE technology appraisal and is not currently planned into any other work programme.
Introduction

Actinic keratosis, or solar keratosis, is a skin condition characterised by thickened, cornified, scaly lesions, developing on areas that are chronically exposed to the sun. Lesions are often asymptomatic but may be sore or itch. According to the British Association of Dermatologists' guideline, between 15% and 25% of actinic keratosis lesions spontaneously resolve over a 1-year period. However, there is a low risk of progression to invasive squamous cell carcinoma (less than 1 in 1000 per annum). It has been estimated that for a person with an average of 7.7 lesions, the probability of at least 1 lesion transforming to squamous cell carcinoma in a 10-year period is approximately 10%.

The prevalence of actinic keratosis increases with age and occurs more commonly in people with fair skin. Prevalence rates of 23% and 19% for people over 60 years in populations in South Wales and Merseyside respectively have been reported (British Association of Dermatologists' guideline).

Guidance on actinic keratosis from the British Association of Dermatologists, the European Dermatology Forum and the Primary Care Dermatology Society pre-dates the availability of ingenol mebutate gel.

Choice of treatment is generally guided by the clinical presentation of the condition and includes general measures, such as the use of emollients and sun protection.

The Primary Care Dermatology Society's guidance notes that treating individual lesions may be appropriate if there are few lesions or larger numbers of widely distributed lesions. Field-directed treatments are recommended for areas of skin that have multiple lesions associated with a background of erythema, telangiectasia and other changes associated with sun-damaged skin. In some situations, 'no treatment' may also be an option.

Therapies for actinic keratosis include ablative procedures (such as cryosurgery, curettage and, in rare cases, excision surgery), photodynamic therapy, and a number of topical treatments (including 5-fluorouracil cream, 5-fluorouracil/salicylic acid solution, diclofenac gel with hyaluronic acid, and imiquimod cream).

The Primary Care Dermatology Society's guidance recommends that actinic keratosis should be managed in the community in most people, and preferably by GPs. Referral to a GP with a specialist interest in dermatology or a consultant dermatologist is recommended when there is diagnostic uncertainty, in more severe cases, if there is suspicion of squamous cell carcinoma, or when a person is at higher risk of developing squamous cell carcinoma.
Product overview

Drug action

Ingenol mebutate is a macrocyclic diterpene ester purified from the *Euphorbia peplus* plant. The mechanism of action of ingenol mebutate gel (Picato) is not fully understood. Both in vivo and in vitro models have suggested a dual mechanism of action, involving induction of local lesion cell death and promotion of an inflammatory response characterised by infiltration of immunocompetent cells. Pharmacokinetic studies suggest that systemic absorption of the drug is absent or below the measurable limit (Picato 500 micrograms/gram and Picato 150 micrograms/gram summaries of product characteristics).

Licensed therapeutic indication

Ingenol mebutate gel is indicated for the cutaneous treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis in adults (Picato 500 micrograms/gram and Picato 150 micrograms/gram summaries of product characteristics).

Course and cost

To treat the trunk or extremities, the content of 1 tube of ingenol mebutate 500 micrograms/gram gel is applied once daily for 2 consecutive days to the affected area.

To treat the face or scalp, the content of 1 tube of ingenol mebutate 150 micrograms/gram gel is applied once daily for 3 consecutive days to the affected area.

Optimal therapeutic effect can be assessed approximately 8 weeks after treatment.

The content of 1 tube covers a single treatment area of 25 cm². The tube is for single-use only and should be discarded after use. Ingenol mebutate gel needs to be refrigerated at 2°C to 8°C.

The cost of 1 treatment course of ingenol mebutate 500 micrograms/gram gel (2-tube pack) or 150 micrograms/gram gel (3-tube pack) is £65 per pack (excluding VAT; cost taken from MIMS, February 2013).
Evidence review

This evidence review is based on a published analysis (Lebwohl et al. 2012) of results from 4 phase III, placebo-controlled randomised trials of ingenol mebutate gel in patients with actinic keratosis (see table 1). Pooled analyses were presented for 2 trials investigating treatment of the face or scalp (studies PEP005-016 and PEP005-025) and 2 trials investigating treatment of the trunk or extremities (studies PEP005-014 and PEP005-028).

- **Design:** all 4 phase III studies were multicentre, randomised, double-blind, vehicle-gel controlled trials.

- **Population:** a total of 547 patients were randomised in the 2 face/scalp studies and 458 patients were randomised in the 2 trunk/extremities studies. The studies were all of a similar design and enrolled patients aged 18 years or older (mean age 65.1 years), with 4 to 8 clinically typical, visible and discrete actinic keratosis lesions in a 25 cm\(^2\) contiguous area. Exclusion criteria included the recent use of other treatments for actinic keratosis, and the presence, within the target treatment area, of: hypertrophic and hyperkeratotic lesions, cutaneous horns or actinic keratosis lesions that had not responded to repeated cryosurgery. Approximately half of the patients in all study groups had a history of skin cancer, and more than 75% had received cryotherapy.

- **Intervention and comparison:** for face/scalp studies, ingenol mebutate 150 micrograms/gram or vehicle gel was self-applied to a single 25 cm\(^2\) contiguous area once daily for 3 consecutive days; for trunk/extremities studies, ingenol mebutate 500 micrograms/gram or vehicle gel was self-applied to a single 25 cm\(^2\) contiguous area once daily for 2 consecutive days.

- **Outcomes:** the primary efficacy measure was complete clearance of all clinically visible actinic keratosis lesions in the target treatment area on day 57. Clearance was visually assessed by study investigators. A secondary outcome was the partial clearance rate, defined as a reduction of 75% or more in the number of clinically visible actinic keratosis lesions in the target treatment area at day 57. An additional secondary outcome that was not specified in the initial study protocol was the median percentage reduction in the number of actinic keratosis lesions. Safety outcomes included skin response at the site of treatment application assessed by a local-skin-response scale. This scale graded 6 different responses (erythema, flaking or scaling, crusting, swelling, vesiculation or pustulation, and erosion or ulceration) on a scale of 0 to 4, giving a maximum composite score of 24, with a higher score indicating greater severity.

**Table 1 Summary of pooled analyses of studies of the face/scalp and the trunk/extremities:**

Lebwohl et al. (2012)
### Pooled analysis of face/scalp studies

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Placebo (vehicle) gel</th>
<th>Ingenol mebutate gel 150 micrograms/gram</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>*<em>Efficacy (ITT analysis</em>)**:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=270</td>
<td>n=277</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Primary outcome: % patients with complete clearance of lesions</strong></td>
<td>3.7% (10/270)(^h)</td>
<td>42.2% (117/277)(^h)</td>
<td>p&lt;0.001 NNT=3</td>
</tr>
<tr>
<td><strong>Secondary outcomes:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% patients with partial clearance of actinic keratosis lesions</td>
<td>7.4% (20/270)(^h)</td>
<td>63.9% (177/277)(^h)</td>
<td>p&lt;0.001 NNT=2</td>
</tr>
<tr>
<td>Median % reduction in number of lesions(n)</td>
<td>0% (range −100% to 100%)(^h) (n=269)</td>
<td>83% (range −50% to 100%)(^h) (n=273)</td>
<td>p value not stated</td>
</tr>
<tr>
<td><strong>Safety</strong>:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=271</td>
<td>n=274</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean maximum composite local-skin-response score (±SD)</td>
<td>1.8 (±1.6)</td>
<td>9.1 (±4.1)</td>
<td>p value not stated</td>
</tr>
<tr>
<td>% patients reporting any adverse event</td>
<td>22.1% (60/271)</td>
<td>37.2% (102/274)</td>
<td>p value not stated</td>
</tr>
<tr>
<td>% patients with adverse event(s) at application site</td>
<td>2.6% (7/271)</td>
<td>19.0% (52/274)</td>
<td>p value not stated</td>
</tr>
<tr>
<td>% patients with adverse event(s) leading to early discontinuation</td>
<td>0.4% (1/271)</td>
<td>0.4% (1/274)</td>
<td>p value not stated</td>
</tr>
</tbody>
</table>

### Pooled analysis of trunk/extremities studies

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Placebo (vehicle) gel</th>
<th>Ingenol mebutate gel 500 micrograms/gram</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>*<em>Efficacy (ITT analysis</em>)**:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=232</td>
<td>n=226</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary outcome: % patients with complete clearance of lesions&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4.7% (11/232)&lt;sup&gt;h&lt;/sup&gt;</td>
<td>34.1% (77/226)&lt;sup&gt;h&lt;/sup&gt;</td>
<td>p&lt;0.001 NNT=4</td>
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<tr>
<td>Secondary outcomes:</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>% patients with partial clearance of actinic keratosis lesions&lt;sup&gt;c&lt;/sup&gt;</td>
<td>6.9% (16/232)&lt;sup&gt;h&lt;/sup&gt;</td>
<td>49.1% (111/226)&lt;sup&gt;h&lt;/sup&gt;</td>
<td>p&lt;0.001 NNT=3</td>
</tr>
<tr>
<td>Median % reduction in number of lesions (n)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0% (range −33% to 100%)&lt;sup&gt;h&lt;/sup&gt; (n=229)</td>
<td>75% (range −25% to 100%)&lt;sup&gt;h&lt;/sup&gt; (n=220)</td>
<td>p value not stated</td>
</tr>
<tr>
<td>Safety&lt;sup&gt;e&lt;/sup&gt;:</td>
<td>n=232</td>
<td>n=225</td>
<td></td>
</tr>
<tr>
<td>Mean maximum composite local skin response score (±SD)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>1.6 (±1.5)</td>
<td>6.8 (±3.5)</td>
<td>p value not stated</td>
</tr>
<tr>
<td>% patients reporting any adverse event</td>
<td>27.2% (63/232)</td>
<td>33.3% (75/225)</td>
<td>p value not stated</td>
</tr>
<tr>
<td>% patients with adverse event(s) at application site&lt;sup&gt;g&lt;/sup&gt;</td>
<td>2.6% (6/232)</td>
<td>12.0% (27/225)</td>
<td>p value not stated</td>
</tr>
<tr>
<td>% patients with adverse event(s) leading to early discontinuation</td>
<td>0.9% (2/232)&lt;sup&gt;h&lt;/sup&gt;</td>
<td>0.9% (2/225)&lt;sup&gt;h&lt;/sup&gt;</td>
<td>p value not stated</td>
</tr>
</tbody>
</table>
Clinical effectiveness

Key data are shown in table 1. In pooled analyses of studies of the face/scalp and trunk/extremities, Lebwohl et al. (2012) found that ingenol mebutate gel was more effective than placebo (vehicle) gel for the primary outcome of complete clearance of all visible actinic keratosis lesions in the target treatment area at day 57. The 4 studies that contributed to the pooled analyses also individually showed a statistically higher rate of complete clearance with ingenol mebutate gel, compared with placebo (p<0.001 in all studies).

In both pooled analyses and individual studies, ingenol mebutate gel was also associated with higher rates of partial clearance of lesions (p<0.001 in all cases). Greater median percentage reductions in lesion numbers were also associated with ingenol mebutate gel.

Safety

In the pooled analyses of the 4 phase III studies, the most common treatment-related adverse events were at the administration site (pain, pruritus and irritation). Local skin responses (erythema, flaking or scaling, crusting, swelling, vesiculation or pustulation, and erosion or ulceration) at the application site, which the authors suggest are an expected effect of topical
treatments for actinic keratosis, were reported separately and assessed at each study visit by a local-skin-response score.

Ingenol mebutate gel was associated with a higher mean maximum composite local-skin-response score compared with vehicle gel in studies of both the face/scalp and trunk/extremities. Scores peaked at day 4 after treating the face or scalp, and at day 3 or day 8 for most patients after treating the trunk or extremities with ingenol mebutate gel. Scores had declined to near-baseline values by day 15 after treatment initiation for the face/scalp and by day 29 for the trunk/extremities. The authors report that there was minimal change in pigmentation and scarring after treatment with either ingenol mebutate or vehicle gel.

**Evidence strengths and limitations**

The pooled analyses showed that ingenol mebutate gel is an effective topical, field-directed treatment for actinic keratosis. However, the included studies had several limitations affecting their usefulness in assessing the place in therapy of ingenol mebutate gel in the NHS.

The comparator in these studies was placebo (vehicle gel). There are no published studies comparing ingenol mebutate gel with other active treatments for actinic keratosis. A Cochrane review (Gupta et al. 2012) considered the efficacy and safety of treatments for actinic keratosis, including ingenol mebutate gel. It concluded that for individual lesions, photodynamic therapy appeared more effective, with a better cosmetic outcome, than cryotherapy. The field-directed treatments, diclofenac gel with hyaluronic acid, 5-fluorouracil cream, imiquimod cream and ingenol mebutate gel, had similar efficacy, but adverse events and cosmetic outcomes varied between treatments. The authors recommended that more direct comparisons between these treatments are needed to determine the best therapeutic approach.

There is also currently an absence of clinical data concerning the repeated use of ingenol mebutate gel after recurrence of lesions; however, a study is ongoing with results expected in 2014.

Actinic keratosis field-changes can often affect a much larger area of skin than the 25 cm² single treatment area specified for ingenol mebutate gel. Clinical data concerning the use of ingenol mebutate gel in an area larger than 25 cm², or in multiple areas, are limited. The summaries of product characteristics for Picato 500 micrograms/gram and Picato 150 micrograms/gram state that, 'In a double-blind, vehicle-controlled study to evaluate systemic exposure, Picato 500 micrograms/gram, from 4 tubes, was applied to a 100 cm² contiguous treatment area daily for 2 consecutive days. Results demonstrated no systemic absorption. Picato 500 micrograms/gram
was well tolerated when applied to a contiguous treatment area of 100 cm² on the trunk and extremities.

As with other topical treatments for actinic keratosis, the presence of local skin responses with ingenol mebutate gel limits the blinding of the studies. This assumes greater importance because the primary outcome relied on a visual assessment of lesions. The European Medicines Agency’s assessment report on Picato commented that, although a visual assessment of lesion clearance was considered a valid endpoint for the phase III studies, there was an absence of histological confirmation. The European Medicines Agency has requested an additional study to be undertaken to investigate histological clearance.

Long-term data are currently limited to observational, 12-month follow-up of 184 patients who had complete clearance of lesions with ingenol mebutate gel in phase III studies (Picato 500 micrograms/gram and Picato 150 micrograms/gram summaries of product characteristics). Approximately 87% of the number of lesions in the treatment area at baseline were clear during this follow-up period; 1 or more lesions developed or recurred in the treatment area in 53.9% of patients in the face/scalp studies and 56.0% of patients in the trunk/extremities studies. Squamous cell carcinoma was reported in no patients (0 of 184 patients) during the 12-month follow-up period.

**Context**

**Treatment alternatives**

Topically-applied treatments licensed for actinic keratosis include 3% diclofenac gel with hyaluronic acid, 5% 5-fluorouracil cream, 0.5% 5-fluorouracil/10% salicylic acid solution, and 3.75% and 5% imiquimod cream. Specific indications for these treatments vary based on the characteristics of lesions.

**Costs of treatment alternatives**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Treatment regimen</th>
<th>Estimated cost for 1 course</th>
</tr>
</thead>
<tbody>
<tr>
<td>3% diclofenac gel with hyaluronic acid</td>
<td>Twice daily for 60 to 90 days</td>
<td>£76.60 (2×50 g tubes)</td>
</tr>
<tr>
<td>Treatment</td>
<td>Regimen</td>
<td>Cost</td>
</tr>
<tr>
<td>-----------</td>
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<tr>
<td><strong>5% 5-fluorouracil cream</strong></td>
<td>Once or twice daily for 3 to 4 weeks</td>
<td>£32.83 (1×40 g tube)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>0.5% 5-fluorouracil/10% salicylic acid solution</strong></td>
<td>Once daily for 6 to 12 weeks</td>
<td>£76.60 (2×25 ml)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>5% imiquimod cream</strong></td>
<td>3 nights a week for weeks. After a 4-week treatment-free period, if lesions persist, repeat treatment for additional 4 weeks</td>
<td>£48.50 (1×4-week treatment, 12 sachets)&lt;sup&gt;c&lt;/sup&gt; £97.00 (2×4-week treatments, 24 sachets)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>3.75% imiquimod cream</strong></td>
<td>Up to 2 sachets, once daily before bedtime for 2 treatment cycles of 2 weeks each, separated by a 2-week no-treatment cycle</td>
<td>£113.00 (use of 1 sachet per day for 2 treatment cycles, 28 sachets)&lt;sup&gt;e&lt;/sup&gt; £226.00 (use of 2 sachets per day for 2 treatment cycles, 56 sachets)&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Ingenol mebutate gel</strong></td>
<td>For face/scalp: 150 micrograms/gram gel applied once daily for 3 days For trunk/extremities: 500 micrograms/gram gel applied once daily for 2 days</td>
<td>£65.00 (all strengths)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Treatment regimens taken from the relevant summary of product characteristics.<br><sup>b</sup> The treatment regimens shown do not imply therapeutic equivalence.<br><sup>c</sup> Costs taken from Drug Tariff, February 2013.<br><sup>d</sup> Costs taken from MIMS, February 2013.<br><sup>e</sup> Manufacturer's list price at time of writing (Meda Pharmaceuticals: personal communication January 2013).
**Estimated impact for the NHS**

*Likely place in therapy*

The choice of treatment for a person with actinic keratosis will largely depend on the clinical presentation of the condition. Ingenol mebutate gel may be an additional option for people in whom field-directed therapies are suitable.

The simple dosing regimen of ingenol mebutate gel and the short duration of the treatment course compared with other self-applied, field-directed agents (with side effects peaking after treatment is completed) may be beneficial in terms of adherence to treatment. This is supported by the high study-completion rates (more than 98%) in the phase III studies.

However, clinical data on the use of more than 1 course of ingenol mebutate gel for 2 or 3 consecutive days, or treatment of more than 1 area of 25 cm$^2$, are not available (*Picato* 500 micrograms/gram and *Picato* 150 micrograms/gram summaries of product characteristics).

The cost of 1 treatment course of ingenol mebutate gel is lower than the cost of 1 course of 3.75% imiquimod cream, higher than 1 course of 5% 5-fluorouracil cream, and either lower or higher than 1 course of 5% imiquimod cream depending on the number of treatment periods needed. However, cost comparisons are dependent on the number of units a person needs to complete a treatment course.

Trials comparing ingenol mebutate gel with other active treatments for actinic keratosis are needed for local decision makers to determine optimal therapeutic approaches.

*Estimated usage*

Estimates for the prevalence of actinic keratosis in the UK population aged over 60 years range from 19% to 23% (*British Association of Dermatologists’ guideline*). Using these data, based on population estimates, approximately 2.4–3 million people over 60 years in England and Wales may be affected by actinic keratosis. It is likely that ingenol mebutate gel may be used in a proportion of people in whom treatment of lesions is considered appropriate. The manufacturer estimates that after launch, uptake will be 35 people in year 1, 102 people in year 2 and 179 people in year 3, in a population of 100,000 (Leo Pharma: personal communication January 2013).
References


European Dermatology Forum. (2011) Guideline on actinic keratoses


Gupta AK, Paquet M, Villanueva E et al. (2012) Interventions for actinic keratoses. Cochrane Database of Systematic Reviews issue 12: CD004415


Primary Care Dermatology Society. (2011, updated January 2013) Clinical guidance – actinic keratosis (syn. solar keratosis)


About this evidence summary

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For information about the process used to develop this evidence summary, see Evidence summaries: new medicines – interim process statement.

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